REMARKS

The Office Action dated April 5, 2010 has been carefully reviewed and the foregoing amendment and the following remarks are made in response thereto. Applicants respectfully request reconsideration of this application and timely allowance of the pending claims.

Status of the Claims

Claims 83, 84, and 87 to 89 are pending in the present application. Applicants have amended claim 83 to positively recite a "whole" test batch and a "whole" standardized batch. Support for these amendments can be found throughout the application as filed. Specific support can be found, for example, at page 11, line 28; page 12, lines 15 and 26; and page 13, line 7. Thus, the above amendments do not introduce any prohibitive new matter.

Claim Rejection under 35 U.S.C. § 103(a)

Claims 83, 84, 87 to 89 are rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over McLaughlin (Drug Information Journal, vol. 32, 513-521, 1998) and Khwaja et al. (U.S. Patent No. 6,113,907) in view of Kojima et al. (Biol. Pharm Bull, 21(4), 426-428), Wallace et al. (Molecular Medicine Today, 1997, vol. 3, 384-389), Friend et al. (U.S. Patent No. 6,218,122), and Xiong et al. (Molecular Breeding, 1998, vol. 4, 129-136). Specifically, the Examiner alleges that it would have been obvious to one skilled in the art at the time of the invention to combine McLaughlin and Khwaja et al. and further replace the bioassay disclosed therein with the assay as described by Kojima et al., Wallace et al., Friend et al., and Xiong et al. to obtain a quality control method as the present application claims.

Applicants have amended claim 83 to positively recite a "whole" test batch and a "whole" standardized batch. In view of the amended claims, Applicants respectfully submit that the Examiner has failed to establish a *prima facie* case of obviousness because there is no motivation for making a modification in neither the cited art nor the common knowledge to arrive at the present quality control method, which comprises, among other things, the steps of (1) exposing a biosystem, such as cell or tissue, to a whole batch of herbal composition, i.e., the whole standardized batch or the whole test batch; and (2) determining a differential gene

expression profile of the exposed biosystem as compared to a control, i.e., an unexposed biosystem. The differential gene expression profile is determined by using a genomic-based bioassay method.

Khwaja et al.:

The Khwaja method is markedly different from the claimed method in at least two aspects: (1) the step of separating/isolating a botanical sample into multiple fractions, and (2) measuring the biological activity of each individual fraction against an enzyme or receptor.

The botanical samples of the present invention, i.e., the standardized and test batches, are each tested as a whole sample without fractionation, while Khwaja et al. fractionate the botanical samples prior to the biological test.

Khwaja et al. do not suggest in any way that the fractionation step be eliminated. In fact, Khwaja et al. repeatedly emphasize the necessity of fractionation of the sample as shown below:

> "The procedure involves separating the aliquot of botanical material into a plurality of marker fractions wherein each of the marker fractions includes at least one of the active components or in some cases one of the inactive components." (underline added, column 13, lines 12 to 14)

> "For establishing a pharmaceutical fingerprint (PharmaPrint®) in accordance with the present invention, the plant is extracted according to the procedure as set forth in FIG. 3 to separate it into major components…" (underline added, column 17, lines 6 to 10)

> "Once the sample extract has been prepared and/or alternatively purchased as a commercially available extract, a portion needs to be subjected to fractional analysis. If the fingerprint has already been established, the sample or aliquot is separated into the same plurality of marker fractions which are present in the standard fingerprint." (underline added, column 22, lines 15 to 20)

> "For some materials only a few marker fractions are required. For other more complex materials, there may be numerous marker fractions." (underline, column 22, lines 24 to 26)

Thus, the specific teachings of fractionation in Khwaja et al. directly contradict the claimed method which tests the whole sample without fractionation.

Furthermore, the biological test performed by Khwaja et al. is mechanism-based bioassay as Khwaja et al. test the biological activity of each individual fraction against an enzyme or receptor, while the present invention measures differential gene expression profile via a genomic-based bioassay. More specifically, the mechanism-based bioassays as conducted by

Khwaja et al. provide only a single data reference point, e.g., IC50, while the differential gene expression data utilized by the claimed method provide an objective molecular fingerprint that can be used for detailed comparisons. It is notable that Khwaja et al. do not mention or allude to a genomic-based bioassay, let alone the use of differential gene expression profile in a quality control method.

McLaughlin:

McLaughlin differs from the claimed method in that McLaughlin uses general bioassays, i.e., non-mechanism-based bioassays, to prescreen the toxicity or inhibitory effects of botanical extracts, while the claimed method uses genomic-based bioassay to obtain the differential gene expression profile of herbal compositions.

It is true that McLaughlin exposes a biosystem to botanical extracts in the bioassay, but McLaughlin's method is not for "determining the differential gene expression profile" of the biosystem as claimed in the present application. Instead, McLaughlin merely measures the general, non-mechanism based, toxicity or inhibitory effects of botanical extracts. For example, in the Brine Shrimp Lethality Bioassay, McLaughlin exposes some brine shrimps to a botanical extracts for 24 hours, then counts the number of surviving brine shrimp, and further uses the number of survivors as an indication of the toxicity of the botanical extracts (Table 1, page 516). This bioassay process is simple and primitive because it does not involve any measuring of enzyme/receptor activity as the mechanism-based bioassay of Khwaja et al. does nor any determination of gene expression levels as the genome-based bioassay does in the instantly claimed invention. In other words, the general bioassays conducted by McLaughlin merely observe the biological effects, such as toxicity or inhibitory effects of the tested sample without inquiring about the mechanistic reasons of the biological effects. These general bioassays are qualitative and not even able to obtain the single quantitative data reference point as the mechanism-based bioassays do, let alone addressing how or why batches of herbal compositions might be different via comparing multiple and complex data points as the present method does.

Importantly, McLaughlin emphasizes the advantages of the general bioassay over the mechanism-based bioassay or any other advanced bioassay method. For example, McLaughlin specifically teaches the following:

> "A rush to very specific, *in vitro,* robotic, mechanism-based bioassays has occurred in recent years. Receptor binding, enzyme inhibition, affinity

> columns, DNA nicking, tubulin inhibition, and so forth usually mimic the effects of some previously known compound having a specific mechanism of action. Researchers must be cautious, however, with mechanism-based assays. The field of vision of such specific microscopes is very narrow; they must be assured that the scope of their bioassays can be wide enough to include diverse and unknown mechanisms as well as new chemical entities. In addition, in such specific bioassays the same extracts have to be analyzed many times, over and over again, before detecting activities. It would seem more logical to prescreen with general bioassays, throw out the negatives, and then employ specific bioassays on the actives.……The four bioassays which are described below are easily adapted as "bench top" procedures for use in natural product chemistry. They are inexpensive, rapid, and technologically simple, requiring little technical training." (Page 514, the paragraph bridging the left and right columns, underline added)

That is, McLaughlin recognizes the shortcomings of using the mechanism-based bioassays in botanical research, and thereby advocates the use of the so-called "general bioassays" due to their technical simplicity. In contrast, recognizing the deficiencies of the mechanism-based bioassays (e.g., of Khwaja et al.), the present invention applies genomic-based bioassays to obtain differential gene expression profiles of herbal compositions. Thus, facing the problems of mechanism-based bioassays, the teachings of McLaughlin, i.e., general bioassays, are directly opposite to the present invention where genomic-based bioassays are applied.

Inasmuch as McLaughlin focuses on the advantages of general bioassays over the mechanism-based bioassays, McLaughlin does not suggest to modify or eliminate the fractionation step of Khwaja et al. In fact, McLaughlin supports the use of fractionation technique as indicated by the following:

> "Extracts must be screened for biological activity, the "active" extracts selected, fractionations directed with bioassays, and the bioactive compounds identified and then exploited." (Page 514, the first paragraph, left column, underline added)

Kojima et al.:

In Kojima et al., a sho-saiko-to composition is exposed to a mouse. However, the Kojima method merely monitors the changes of the cytochrome P-450 mRNA level in the mouse liver and does not involve the steps of exposing both the test and standarized batches of herbal compositions to the biosystem to obtain and compare two differential gene expression profiles as claimed in the present application. Furthermore, Kojima et al. use the disclosed techniques for

the purpose of determining the molecular mechanism of Kampo medicine (see the last sentence of the Abstract). Kojima et al. are completely silent as to whether the disclosed method can be used for the purpose of controlling the quality of herbal compositions, let alone modifying the disclosed method for that purpose.

Wallace:

Wallace is a review article discussing the use of genomic-based technology for diagnostics and research in general terms. However, Wallace does not disclose, suggest, or contemplate the use of genomic-based technology for controlling the quality of herbal compositions.

Xiong et al.:

Xiong et al. use differential display analysis to assess the patterns of differential gene expression in hybrids relative to their parents in certain rice plants. However, Xiong et al. focus on the genetics and gene expression profile of the rice plants themselves for plant identification. That is, the differential gene expression in Xiong et al. is that of botanical materials, i.e., rice plants. In contrast, the differential gene expression in the claimed method is that of a biosystem exposed to botanical materials, such as cell or tissue, not that of the botanical materials themselves. Furthermore, Xiong et al. do not suggest or contemplate obtaining the differential gene expression profile of any biosystem, such as cell or tissue, for the purpose of quality control in producing herbal preparations.

Friend et al.:

Friend et al. disclose a method for determining or monitoring the progression of disease states or the efficacy of a therapeutic regimen by measuring RNA or protein abundances or activities in a patient. The disclosures of Friend et al. are not even relevant to the quality control of herbal compositions, let alone the use of the disclosed techniques for controlling the quality of herbal compositions.

In view of the foregoing, the cited references fail to provide any teaching or suggestion which would motivate one skilled in the art to combine and modify those disclosures in such a particular manner to arrive at the claimed method. Specifically, the methods of the two primary references are not suitable for combination because Khwaja et al. discloses fractionation of a botanical sample and determination of the biological activity of each individual fraction via

mechanism-based bioassays, while McLaughlin points out the problems of the mechanism-based bioassays and prefers the general bioassays to the mechanism-based bioassays in botanical research. Moreover, as discussed above, the secondary references, solely or in combination, merely contain various disclosures in discrete pieces and fail to cure the deficiencies and inconsistencies of the two primary references. For example, none of the secondary references is relevant to quality control of producing herbal compositions. In addition, none of the secondary references suggest the modification/elimination of fractionation as disclosed by Khwaja et al. nor the application of exposing a biosystem to both a test batch and a standarized batch of herbal compositions to obtain and compare the resulting differential gene expression profiles. Thus, Applicants respectfully submit that from both a legal and technical basis the alleged combination of "prior art" is improper.

Common Knowledge:

As stated in the Declaration under 37 C.F.R. §1.132 by Dr. Dan Theodorescu dated March 7, 2005 ("the Declaration", a copy is enclosed), Dr. Theodorescu (paragraphs 5 and 6, pages 2 to 7), a person of ordinary skill in the art who was aware of gene expression technology and the need for botanical quality control, did not envision applying genomic-based assays to botanical quality control in such a particular way to arrive at the claimed method at the priority filing date of the present application.

Therefore, there is no disclosure or suggestion in neither the cited references nor the common knowledge which would motivate one skilled in the art to combine and modify the prior art methods in a particularly manner to obtain the present invention.

Due to the lack of a motivation for making modification of the prior art methods in both the cited references and the common knowledge in the art, it logically follows that the Examiner has improperly gleaned from Applicant's own application and exercised the impermissible hindsight to reconstitute a motivation to arrive at this clearly erroneous conclusion of obviousness. In *Graham*, the Supreme Court has cautioned against using hindsight whereby the teachings of the invention are read into the prior art. *Graham v. John Deere Co.*, 383 U.S. 1, 36 (1966). More recently, the Supreme Court recognized in *KSR* that "hindsight bias" and "ex post reasoning" as inappropriate in determination of obviousness. *KSR Int'l Co. v. Teleflex, Inc.*, 127 S. Ct. 1727, 1742 (2007).

No Reasonable Expectation of Success:

The §103 rejection also fails because one skilled in the art would not have a reasonable expectation of success even if, for the sake of argument, the prior art methods are combined and modified in the way as allegedly by the Examiner. In the Declaration, Dr. Theodorescu cited a scientific paper co-authored by himself and published in 2003 (Bigler, et al. Oncogene, 22, 2003, 1261-1271, a copy is enclosed as Exhibit B of the Declaration) and further stated that the utility of gene expression profiles for quality control of botanicals as suggested by the paper was actually an afterthought indicating that the authors did not have a reasonable expectation of success at the time of the research, i.e., several years after the filing of the present application (see paragraph 6, pages 6 and 7). Specifically, the 2003 paper characterized the results from comparing the differential gene expression profiles of two herbal compositions as "surprising". (See Bigler et al. page 1266, the first full paragraph below Table 3 in right column)

Secondary Considerations:

Moreover, there are long felt but unresolved needs as well as failure of others for the development of a method of controlling the quality of herbal compositions.

Specifically, despite the fact that herbal medicines have been used for many centuries in the treatment of various diseases, more advanced development of herbal medicines has been hindered by the unique problem of unpredictable variability of herbal medicines due to the lack of quality control method (Khwaja et al., page 1, line 10 to page 2, line 7, and page 7, line 22 to page 8, line 6 of the present application; and column 2, line 40 to column 3, line 2). To resolve this long felt need for a quality control method, a great deal of effort has been directed to the separation and isolation of the biologically active components from botanical materials. But this purification approach diminishes the benefits of complex and synergistic biological activity provided by naturally occurring botanical material (Khwaja et al., column 3, lines 3 to 43). Khwaja et al. attempt to provide a method for producing pharmaceutical grade of St. John's Wort by using compositional and activity fingerprints. However, as discussed above, Khwaja et al. applies fractionation technique to process the samples, i.e., separating and isolating the samples into multiple fractions. Thus, the Khwaja method does not overcome the disadvantage of the purification approach.

As shown by paragraph 5 (pages 2 to 4) of the Declaration, others have also failed in their attempts to resolve the problem. For example, despite the promising initial clinical data, the clinical trial of BotanicLab's herbal medicine, namely, PC-SPES, was halted due to quality control problems.

In addition, inventors of the present application have recently published an article – Tilton et al., "A Comprehensive Platform for Quality Control of Botanical Drugs (PhytomicsQC): a Case Study of Huanqin Tang (HQT) and PHY906" Chinese Medicine, 2010, 5:30 (a copy is enclosed). This article describes an embodiment of the instantly claimed method and its application in controlling the quality of herbal compositions. The article concludes that PhytomicsQC, i.e., one embodiment of the claimed method, is a first generation platform for botanical quality control (page 14, the Conclusion section). The fact that an article with such a conclusion was published in a peer-reviewed and internationally renowned journal of herbal medicines provides additional evidence of secondary considerations to support non-obviousness of the claimed invention.

In *Graham v. John Deer Co. of Kansas City*, 383 U.S. 1, 17-18, the United States Supreme Court set out an objective analysis for applying §103 rejections where secondary considerations, such as long felt but unresolved needs and failure of others, are considered as important factors against finding of obviousness. In view of the above-discussed long felt but unresolved needs and failure of others in developing a quality control method for assessing herbal compositions, Applicants respectfully request reconsideration and withdrawal of the present §103 rejection.

In view of the lack of a motivation for making modifications, the lack of a reasonable expectation of success, and the showing of the secondary considerations, Applicants respectfully submit that a *prima facie* case of obviousness has not been established.

Conclusion

In view of the foregoing remarks, Applicants respectfully request withdrawal of the outstanding rejection and early notice of allowance to that effect. Should the Examiner believe that a telephonic interview would expedite prosecution and allowance of this application, he is encouraged to contact the undersigned at his convenience.

Except for issue fees payable under 37 C.F.R. § 1.18, the Commissioner is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. §§ 1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account No.50-1283. This paragraph is intended to be a **CONSTRUCTIVE PETITION FOR EXTENSION OF TIME** in accordance with 37 C.F.R. § 1.136(a)(3).

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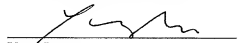
By: 

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